Mercurated Derivatives of Morpholine, Tetrahydro-1,4-thiazine, and Hexahydropyrazine. Synthesis of Substituted Morpholines, Unsaturated Aminoethers, Aminothioethers, and Diamines

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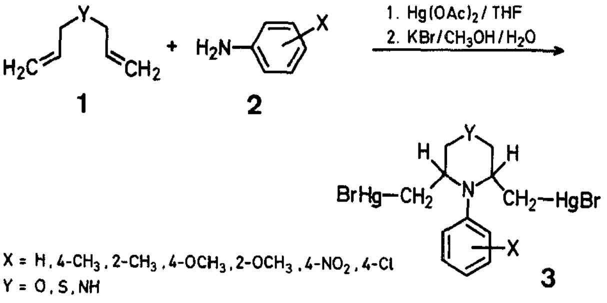
The aminomercuration-demercuration of dienes is a suitable method for the synthesis of *N*-heterocyclic systems[1,2]. However, the demercuration process can lead almost exclusively to δ-unsaturated amines[3] under certain reduction conditions. The simplicity of the reaction and the high yields of heterocyclic products obtained by this procedure prompted us to study its application to the synthesis of mercurated heterocyclic systems containing two hetero atoms, one of them being nitrogen, and their further demercuration.

When mercury(II) acetate is allowed to react at room temperature with diallyl ether (**1**, Y = O), diallyl sulfide (**1**, Y = S), or diallylamine (**1**, Y = NH) in the presence of primary arenamines[4] (**2**), mercurated derivatives of morpholine, tetrahydro-1,4-thiazine, and hexahydropyrazine are formed. These compounds may be characterized and isolated as the bis-[bromomercurio] derivatives **3** upon anion exchange by treatment of the crude reaction mixture with potassium bromide.



Sodium borohydride reduction[5] of compounds **3** with retention of the ring skeleton can only be achieved in the case of the morpholine derivatives (**3**, Y = O)[6] by carrying out the reduction in alkaline medium (pH 10). The morpholine derivatives **4** thus obtained are mixtures of two isomers,

Table 1. 3,5-Bis[bromomercuriomethyl]-4-phenylmorpholines (**3**, Y = O) and -tetrahydro-1,4-thiazines (**3**, Y = S), 2,6-Bis[bromomercuriomethyl]-1-phenylhexahydropyrazines (**3**, Y = NH)

3	Y	X	Reaction conditions Ar—NH$_2$/Hg$^{\oplus\oplus}$	Time	Yield[a] [%]	m.p. (solvent)	Molecular formula[b]	I.R. (nujol) [cm^{-1}] ν_{NH}	ν_{CO}	ν_{arom}
a	O	H	8/1	5 min	100	130–131° (dec) (dioxan/methanol)	$C_{12}H_{15}Br_2Hg_2NO$ (750.2)	—	1100	3050, 1570, 1550, 1490, 780, 730
b	S	H	8/1	3 h	100	70–72° (dec)[c]	$C_{12}H_{15}Br_2Hg_2NS$ (766.3)	—	—	3020, 1600, 1570, 1500, 760, 700
c	NH	H	5/1	5 min	100	108–110° (dec)[c]	$C_{12}H_{16}Br_2Hg_2N_2$ (749.3)	3300[d]	—	3040, 1600, 1550, 1500, 760, 710
d	O	4-CH$_3$	4/1	3 h	100	78–80° (dec) (ethanol)	$C_{13}H_{17}Br_2Hg_2NO$ (764.3)	—	1100	3050, 1620, 1520, 1510, 820
e	S	4-CH$_3$	4/1	22 h	85	77–79° (dec)[c]	$C_{13}H_{17}Br_2Hg_2NS$ (780.3)	—	—	3025, 1615, 1520, 820
f	NH	4-CH$_3$	3/1	40 min	99	113–115° (dec)[c]	$C_{13}H_{18}Br_2Hg_2N_2$ (763.3)	3300	—	3040, 1610, 1510, 820
g	O	4-OCH$_3$	2/1	7 h	81	99–100° (dec)[c]	$C_{13}H_{17}Br_2Hg_2NO_2$ (780.3)	—	1100	3050, 1600, 1560, 1510, 830
h	S	4-OCH$_3$	3/1	25 h	83	98–100° (dec)[c]	$C_{13}H_{17}Br_2Hg_2NOS$ (796.3)	—	—	3050, 1610, 1580, 1520, 830
i	NH	4-OCH$_3$	3/1	1 h	100	108–110° (dec)[c]	$C_{13}H_{18}Br_2Hg_2N_2O$ (779.3)	3280[d]	—	3040, 1610, 1510, 840
j	O	4-NO$_2$	2.5/1	2 d	80	210° (dec) (methanol)	$C_{12}H_{14}Br_2Hg_2N_2O_3$ (795.2)	—	1100[e]	3020, 1580, 1560, 1490, 850
k	S	4-NO$_2$	3/1	4 d	62	134–135° (dec)[c]	$C_{12}H_{14}Br_2Hg_2N_2O_2S$ (811.3)	—	—[f]	3020, 1600, 1590, 1500, 830
l	NH	4-NO$_2$	3/1	20 h	68	104–105° (dec)[c]	$C_{12}H_{15}Br_2Hg_2N_3O_2$ (794.3)	3300[d]	—[g]	3020, 1600, 1500, 840
m	O	4-Cl	3/1	30 min	96	115–117° (dec) (acetone)	$C_{12}H_{14}Br_2ClHg_2NO$ (784.7)	—	1100	3050, 1600, 1580, 1500, 830
n	S	4-Cl	3/1	3 h	98	60–62° (dec)[c]	$C_{12}H_{14}Br_2ClHg_2NS$ (800.7)	—	—	3060, 1590, 1490, 820
o	NH	4-Cl	2/1	30 min	96	110–112° (dec)[c]	$C_{12}H_{15}Br_2ClHg_2N_2$ (783.7)	3300[d]	—	3020, 1600, 1500, 835
p	O	2-CH$_3$	4/1	5 h	100	68–70° (dec) (THF/methanol)	$C_{13}H_{17}Br_2Hg_2NO$ (764.3)	—	1100	3050, 1600, 1580, 1510, 760, 730
q	O	2-OCH$_3$	4/1	3 h	87	75–77° (dec) (THF/methanol)	$C_{13}H_{17}Br_2Hg_2NO_2$ (780.3)	—	1100	3050, 1600, 1580, 1500, 770, 730

[a] Based on diene **1**.

[b] All products **3** gave satisfactory microanalyses: N, ±0.03; Hg, ±0.31; exception: **3k, 3l**; Hg, ±0.42.

[c] These compounds could not be recrystallized.

[d] Very weak.

[e] $\nu_{NO_2} = 1460, 1300\ cm^{-1}$.

[f] $\nu_{NO_2} = 1480, 1310\ cm^{-1}$.

[g] $\nu_{NO_2} = 1470, 1310\ cm^{-1}$.

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Table 2. 3,5-Dimethyl-4-phenylmorpholines (**4**, Y = O)

4	X	Reaction time	Yield [%] **4**[a]	Yield [%] Hg^0[b]	b.p./ 0.001 torr	Molecular[c] formula	Isomer ratio [%] from G.L.C.[d] (retention time [min])	Isomer ratio [%] from ¹H-N.M.R.[e]	I.R. (film) [cm⁻¹] ν_{CH}	I.R. (film) [cm⁻¹] ν_{C-O}	I.R. (film) [cm⁻¹] ν_{arom}	¹H-N.M.R. (CCl_4, 90 MHz) δ [ppm]
a	H	4 h	71	82	55–60°	$C_{12}H_{17}NO$ (191.3)	41 (2.08) 59 (2.27)	39 61	2900, 1440, 1370	1100	3500, 1570, 1490, 790, 730	0.7, 0.9 (2d, J=6 Hz, 6H); 3.0–4.0 (m, 6H); 7.0 (m, 5H)
b	4-CH_3	1 d	74	78	57–61°	$C_{13}H_{19}NO$ (205.3)	56 (2.01) 44 (2.20)	54 46	2900, 1460, 1380	1120	3050, 1600, 1510, 850	0.6, 0.85 (2d, J=6 Hz, 6H); 2.3 (s, 3H); 2.8–3.9 (m, 6H); 7.0 (m, 4H)
c	2-CH_3	2 d	83	82	60–65°	$C_{13}H_{19}NO$ (205.3)	45 (1.88) 55 (2.04)	39 61	2900, 1470, 1380	1100	3060, 1610, 1590, 1500, 770, 740	0.55, 0.65 (2d, J=6 Hz), 1.0 (d, J=7 Hz) (total 6H); 2.29, 2.31 (2s, 3H); 2.8–3.9 (m, 6H); 7.0 (m, 4H)
d	4-OCH_3	2 h	93	84	64–70°	$C_{13}H_{19}NO_2$ (221.3)	57 (2.44) 43 (2.68)	56 44	2900, 1450, 1360	1100	3050, 1600, 1500, 850	0.6, 0.85 (2d, J=6 Hz, 6H); 2.8–3.8 (m with s at 3.7, 9H); 6.8 (m, 4H)
e	2-OCH_3	15 h	55	63	63–68°[f]	$C_{13}H_{19}NO_2$ (221.3)	9 (2.76) 91 (3.07)	10 90	2900, 1460, 1380	1100	3050, 1600, 1510[g]	0.65 (d, J=6 Hz), 0.95 (d, J=7 Hz)[h] (total 6H); 3.1–4.1 (m with s at 3.85, 9H); 6.95 (m, 4H)
f	4-NO_2	6 d	52	—[i]	85–90°	$C_{12}H_{16}N_2O_3$ (236.3)	39 (4.07) 61 (4.25)	40 60	2900, 1450, 1360	1110	3100, 1610, 1500[j] 830	1.05, 1.3 (2d, J=6 Hz, 6H); 3.3–4.1 (m, 6H); 6.8, 8.0 (2m, 4H)

[a] Based on mercury precipitated.

[b] Hg precipitated.

[c] All products **4** gave satisfactory microanalyses: C, ±0.35; H, ±0.09; N, ±0.05.

[d] Chromosorb OV-101; 1.5 m; initial temperature 160°, final temperature 260°, Δ_{temp} = 24°/min; flow rate 0.5 ml/sec.

[e] Relative to integral of CH—C$\underline{H}_3$ signals.

[f] m.p. 57–59°.

[g] In CCl_4.

[h] In $CDCl_3$.

[i] Hg could not be isolated; yield of **4f** based on **3f**.

[j] ν_{NO_2} = 1500, 1340 cm⁻¹.

Table. Allyl 2-Anilinopropyl Ethers (**5**, Y = O), Allyl 2-Anilinopropyl Sulfides (**5**, Y = S), *N*-Allyl-*N'*-phenyl-1,2-propanediamines (**5**, Y = NH)

5	Y	X	Reaction time	Yield [%] **5**[a]	Yield [%] Hg[b]	b.p./ 0.001 torr[c]	Molecular formula[d]	I.R. (film) cm⁻¹ ν_{NH}	I.R. (film) cm⁻¹ ν_{CH}	I.R. (film) cm⁻¹ $\nu_{C=C}$	I.R. (film) cm⁻¹ ν_{C-O}	I.R. (film) cm⁻¹ ν_{arom}	¹H-N.M.R. (CCl_4, 90 MHz) δ [ppm]
a	O	H	15 min	51	88	60–64°	$C_{12}H_{17}NO$ (191.3)	3400	2900, 1440, 1320	1650	1100	3100, 1600, 1500, 750, 700	1.2 (d, J=6 Hz, 3H); 3.2–3.7 (m with d at 3.35, J=2 Hz, 4H); 3.9 (d, J=6 Hz, 2H); 5.2 (m, 2H); 5.8 (m, 1H); 6.8 (m, 5H)
b	S	H	3 h	46	81	75–80°	$C_{12}H_{17}NS$ (207.3)	3400	2900, 1440, 1380	1650	—	3060, 1610, 1510, 760, 700	1.25 (d, J=6 Hz, 3H); 2.5 (m, 2H); 3.0 (d, J=6 Hz, 2H); 3.3–3.7 (m with s at 3.45, 2H); 4.9 (m, 2H); 5.7 (m, 1H); 6.3–7.2 (m, 5H)
c	NH	H	3 d	49	86	61–65°	$C_{12}H_{18}N_2$ (190.3)	3350	2900, 1460, 1380	1650	—	3040, 1610, 1510, 760, 700	1.15 (d, J=6 Hz, 3H); 2.6 (m, 4H); 3.2 (d, J=5 Hz, 2H); 3.5 (m, 1H); 5.1 (m, 2H); 5.8 (m, 1H); 6.3–7.2 (m, 5H)
d	O	4-CH_3	10 min	43	66	70–75°	$C_{13}H_{19}NO$ (205.3)	3400	2900, 1440, 1310	1630	1100	3020, 1600, 1520, 810	1.2 (d, J=6 Hz, 3H); 2.2 (s, 3H); 3.2–3.7 (m, 4H); 3.9 (d, J=6 Hz, 2H); 5.2 (m, 2H); 5.8 (m, 1H); 6.7 (m, 4H)

e	S	4-CH_3	2 d	60	72	75–80°	$C_{13}H_{19}NS$ (221.3)	3400	2900, 1450, 1380	1650	—	3050, 1620, 1580, 1520, 810	1.25 (d, J=6 Hz, 3H); 2.2 (s, 3H); 2.5 (m, 2H); 3.0 (d, J=7 Hz, 2H); 3.2–3.8 (m, 2H); 4.9 (m, 2H); 5.7 (m, 1H); 6.3–7.1 (m, 4H)
f	NH	4-CH_3	6 d	37	70	69–73°	$C_{13}H_{20}N_2$ (204.3)	3360	2900, 1460, 1380	1650	—	3060, 1620, 1520, 820	1.15 (d, J=6 Hz, 3H); 2.2 (s, 3H); 2.6 (m, 4H); 3.2 (d, J=5 Hz, 2H); 3.4 (m, 1H); 5.1 (m, 2H); 5.7 (m, 1H); 6.3–7.0 (m, 4H)
g	O	4-OCH_3	10 min	48	91	75–80°	$C_{13}H_{19}NO_2$ (221.3)	3400	2900, 1450, 1380	1650	1100	3050, 1600, 1560, 1520, 830	1.2 (d, J=6 Hz, 3H); 3.2–3.7 (m with s at 3.65, 7H); 3.9 (d, J=6 Hz, 2H); 5.2 (m, 2H); 5.8 (m, 1H); 6.5 (m, 4H)
h	S	4-OCH_3	1 d	37	86	78–82°	$C_{13}H_{19}NOS$ (237.3)	3400	2900, 1460, 1380	1640	—	3050, 1610, 1520, 830	1.25 (d, J=6 Hz, 3H); 2.5 (m, 2H); 3.05 (d, J=7 Hz, 2H); 3.1–3.6 (m with s at 3.2, 2H); 3.7 (s, 3H); 4.9 (m, 2H); 5.7 (m, 1H); 6.5 (m, 4H)
i	NH	4-OCH_3	4 d	24	74	73–77°	$C_{13}H_{20}N_2O$ (220.3)	3360	2900, 1460, 1380	1640	—	3080, 1630, 1530, 830	1.1 (d, J=6 Hz, 3H); 2.6 (m, 2H); 2.9 (broad, 2H); 3.15 (d, J=5 Hz, 2H); 3.35 (m, 1H); 3.65 (s, 3H); 5.1 (m, 2H); 5.8 (m, 1H); 6.5 (m, 4H)
j	O	4-NO_2	2 d	39[e]	—[e]	91–96°	$C_{12}H_{16}N_2O_3$ (236.3)	3400	2900, 1460, 1380	1630	1100	3100, 1600, 1540[f], 1500, 830	1.25 (d, J=6 Hz, 3H); 3.4 (d, J=4 Hz, 2H); 3.65 (m, 1H); 3.9 (d, J=5 Hz, 2H); 4.9 (broad, 1H); 5.2 (m, 2H); 5.8 (m, 1H); 6.5, 7.9 (2m, 4H)
k	S	4-NO_2	8 d	33[e]	—[e]	100–104°	$C_{12}H_{16}N_2O_2S$ (252.3)	3380	2900, 1460, 1380	1640	—	3060, 1600, 1500[g], 840	1.35 (d, J=6 Hz, 3H); 2.6 (m, 2H); 3.1 (d, J=7 Hz, 2H); 3.8 (m, 1H); 4.6 (broad, 1H); 5.0 (m, 2H); 5.8 (m, 1H); 6.5, 8.0 (2m, 4H)
l	O	4-Cl	10 min	79	78	71–75°	$C_{12}H_{16}ClNO$ (225.7)	3400	2900, 1460, 1380	1640	1100	3100, 1600, 1500, 820	1.2 (d, J=6 Hz, 3H); 3.1–3.8 (m, 4H); 3.9 (d, J=6 Hz, 2H); 5.2 (m, 2H); 5.8 (m, 1H); 6.7 (m, 4H)
m	S	4-Cl	5 d	29	70	81–85°	$C_{12}H_{16}ClNS$ (241.8)	3380	2900, 1460, 1380	1650	—	3060, 1600, 1500, 830	1.2 (d, J=6 Hz, 3H); 2.55 (m, 2H); 3.05 (d, J=7 Hz, 2H); 3.5 (m, 1H); 4.0 (broad, 1H); 5.0 (m, 2H); 5.7 (m, 1H); 6.3–7.3 (m, 4H)
n	NH	4-Cl	5 d	21	68	74–78°	$C_{12}H_{17}ClN_2$ (224.7)	3360	2900, 1450, 1370	1650	—	3100, 1600, 1500 830	1.1 (d, J=6 Hz, 3H); 2.6 (m, 2H); 2.7–3.7 (m with d at 3.15, J=5 Hz, 5H); 5.1 (m, 2H); 5.7 (m, 1H); 6.3–7.1 (m, 4H)
o	O	2-CH_3	16 h	35	90	70–74°	$C_{13}H_{19}NO$ (205.3)	3400	2900, 1460, 1380	1640	1100	3050, 1600, 1590, 1520, 760	1.2 (d, J=6 Hz, 3H); 2.1 (s, 3H); 2.9–3.8 (m with d at 3.45, J=6 Hz, 4H); 3.9 (d, J=6 Hz, 2H); 5.2 (m, 2H); 5.9 (m, 1H); 6.8 (m, 4H)
p	O	2-OCH_3	5 min	76	90	78–82°	$C_{13}H_{19}NO_2$ (221.3)	3400	2900, 1450, 1360	1650	1100	3080, 1610, 1530, 750	1.2 (d, J=6 Hz, 3H); 3.2–3.8 (m with s at 3.7, 6H); 3.85 (d, J=6 Hz, 2H); 4.1 (broad, 1H); 5.2 (m, 2H); 5.8 (m, 1H); 6.5 (m, 4H)

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[a] Based on mercury precipitated.

[b] Hg precipitated.

[c] Purity >95 %, according to G.L.C. analysis (Chromosorb OV-101).

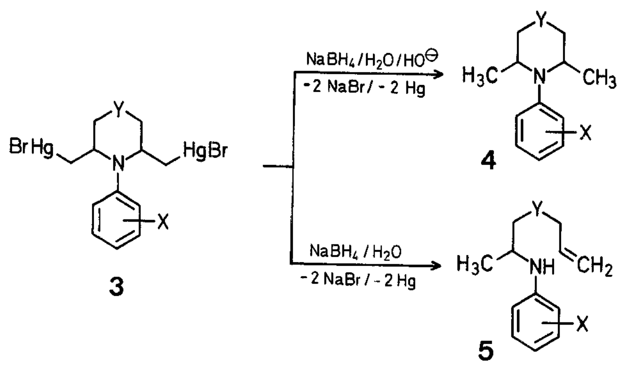
[d] All products **5** gave satisfactory microanalyses: C, ±0.35; H, ±0.11; N, ±0.08.

[e] Hg could not be isolated; yield of **5j** and **5k** based on **3**.

[f] ν_{NO_2}=1550, 1330 cm^{-1}.

[g] ν_{NO_2}=1500, 1300 cm^{-1}.

probably *cis*- and *trans*-stereoisomers[7]. When the reduction of compounds **3** is carried out in neutral medium (pH 7) or in the case of Y=S or NH also in alkaline medium, cleavage of the C—N bond occurs to give allyl 2-aminoalkyl ethers (**5**, Y=O), allyl 2-aminoalkyl sulfides (**5**, Y=S), or *N*-allyl-*N*′-aryl-1,2-propanediamines (**5**, Y=NH)[8].



3,5-Bis[bromomercuriomethyl]-4-phenylmorpholine (3a); Typical Procedure:

Mercury(II) acetate (19.08 g, ~60 mmol) is added with good stirring to a solution of diallyl ether (3.6 ml, 30 mmol) and aniline (50 ml) in tetrahydrofuran (100 ml). After 5 min, the solvent and the excess of amine are removed under reduced pressure (0.1 torr) and the residue is stirred with a solution of potassium bromide (12.0 g) in methanol/water (4:1; 250 ml). The precipitated product (22.5 g, 100%) is isolated by suction and recrystallized from dioxan/methanol (5:1); yield: 18 g (80%); m.p. 130° (dec).

$C_{12}H_{15}Br_2Hg_2NO$	calc.	N 1.87	Hg 53.47
(750.2)	found	1.85	53.50

3,5-Dimethyl-4-phenylmorpholine (4a); Typical Procedure:

3,5-Bis[bromomercuriomethyl]-4-phenylmorpholine (**3a**; 10 g, 13.2 mmol) is suspended in tetrahydrofuran (50 ml) + aniline (20 ml) + 0.5 normal aqueous sodium hydroxide (100 ml). Then, a solution of sodium borohydride (0.57 g, ~15 mmol) in 2.5 normal aqueous sodium hydroxide (20 ml) is added with stirring. After 4 h, the mixture is extracted with ether and the extract washed with water. The organic layer is dried with anhydrous sodium sulfate, the ether is evaporated at 15 torr, and the oily residue is distilled in vacuo; yield: 1.4 g (71%, based on mercury precipitated); b.p. 55–60°/0.001 torr.

$C_{12}H_{17}NO$	calc.	C 75.35	H 8.96	N 7.32
(191.3)	found	75.10	8.87	7.27

Allyl 2-Anilinopropyl Ether (5a); Typical Procedure:

A solution of sodium borohydride (1.7 g, ~42 mmol) in 0.5 normal aqueous sodium hydroxide (30 ml) is added slowly over 10 min to a stirred suspension of 3,5-bis[bromomercuriomethyl]-4-phenylmorpholine (**3a**; 13.5 g, ~18.2 mmol) in tetrahydrofuran (50 ml) + aniline (20 ml) + water (75 ml). The resultant mixture is extracted with ether, the extract is dried with sodium sulfate, and the solvent is removed at 15 torr. The residue is distilled in vacuo; yield: 1.5 g (51%, based on mercury precipitated); b.p. 60–64°/0.001 torr; purity (by G.L.C.): 96%.

$C_{12}H_{17}NO$	calc.	C 75.35	H 8.96	N 7.32
(191.3)	found	75.20	8.85	7.40

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[2] V. Gómez Aranda, J. Barluenga, G. Asensio, M. Yus, *Tetrahedron Lett.* **1972**, 3621.

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[4] Primary aliphatic amines yield amine-mercury(II) complexes instead of products of addition of the double bond under similar reaction conditions: J. Barluenga, C. Nájera, M. Yus, *An. Quím.*, in press.

[5] H. C. Brown, P. Geoghegan, *J. Am. Chem. Soc.* **89**, 1522 (1967).

[6] Other demercuration methods attempted such as Li/THF or Na/NH_3 reduction led to negative results.

[7] Separation and identification of the isomers **4** is currently being carried out.

[8] Compounds of the type **5** cannot be obtained by monomercuration-demercuration of the starting diene **1**: C. Nájera, private communication.